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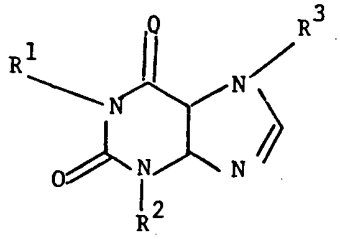
(54) PHARMACEUTICAL COMPOSITIONS, ALKENYL XANTHINES CONTAINED THEREIN AND PROCESSES FOR THEIR PREPARATION

(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised under the laws of the Federal Republic of Germany, of 6230 Frankfurt/Main-80, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel pharmaceutical compositions comprising xanthine derivatives, to novel xanthine derivatives, and processes for their preparation.

A process for the hydration of (ω - 1)-alkenyl - xanthine derivatives of general formula

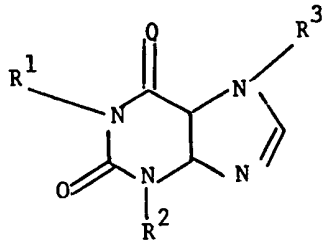


(I)

in the presence of a catalyst to form corresponding (ω - 1) - hydroxyalkyl - xanthines is known. In the above formula one of R^1, R^2 and R^3 represents an (ω - 1) - alkenyl group having from 4 to 8 carbon atoms and the remainder of R^1, R^2 and R^3, which may be the same or different, each represents a straight-chained or branched alkyl group having from 1 to 12 carbon atoms, and R^1 and/or R^3 may also represent hydrogen atoms, with the proviso however that at least one of R^1, R^2 and R^3 has at least 5 carbon atoms. (ω-1) - -Hydroxyalkyl - xanthines are suitable for use in medicine, especially for the treatment of circulation disorders of blood in the brain.

We have now found that corresponding alkenyl-xanthines, and especially (ω - 1-alkenyl - xanthines, exhibit interesting pharmacological properties and in particular a vascular circulation-assisting activity, an activity of promoting blood perfusion, especially in the cerebrovascular region.

According to one aspect of the present invention there is provided a pharmaceutical composition comprising as active ingredient at least one compound of formula



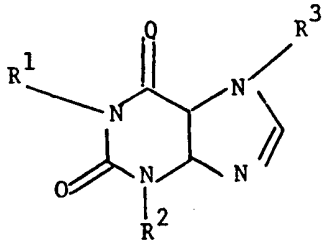
(I)

(wherein R^1 represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or an alkenyl group having from 4 to 8 carbon atoms; and R^2 and R^3, which may be the same or different, each represents an alkyl group having from 1 to 12 carbon atoms or an alkenyl group having from 4 to 8 carbon atoms; with the proviso that at least one of R^1, R^2 and R^3 represents an alkenyl group having from 4 to 8 carbon atoms) in association with a pharmaceutical carrier or excipient. Any of the alkyl and alkenyl groups may be straight-chained or branched.

Preferred compositions are those comprising compounds of formula I in which at least one alkenyl group is an (ω - 1) - alkenyl group. Also preferred are those compositions containing compounds of formula I in which one of R^1, R^2 and R^3 is an (ω - 1) - alkenyl radical with 4 to 8 carbon atoms in which the carbon

atom of the double bond is separated from the xanthine nucleus by at least one saturated carbon atom and both of the other groups are methyl, however R^1 may also be a hydrogen atom, but R^2 always represents a methyl or an alkenyl group. One of R^1, R^2 and R^3 in the compound of formula I is preferably a straight-chained (ω - 1) - alkenyl radical with 5 to 8 carbon atoms. Advantageously one of R^1 and R^3 is a straight-chained (ω - 1)-alkenyl group having from 4 to 8 carbon atoms and the other is a methyl group.

According to a further feature of the invention there are provided compounds of general formula



(I')

wherein R^1 represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or an alkenyl group having from 4 to 8 carbon atoms; and R^2 and R^3, which may be the same or different, each represents an alkyl group having from 1 to 12 carbon atoms or an alkenyl group having from 4 to 8 carbon atoms; with the proviso that at least one of R^1, R^2 and R^3 represents an alkenyl group having from 4 to 8 carbon atoms, R^1 is other than a but-3-enyl, pent-4-enyl or 2 - methyl-but - 3 - enyl group when R^2 and R^3 both represent methyl groups, R^1 is other than a hex-5-enyl group when R^2 represents a methyl group and R^3 represents a methyl, ethyl, propyl, butyl, isobutyl, decyl or hex-5-enyl group, R^1 is other than a methyl group when R^2 is a methyl group and R^3 is a 2 - methyl-but - 3 - enyl, but-3-enyl, pent-4-enyl, hex-5-enyl or hept-6-enyl group, R^1 is other than a hydrogen atom when R^2 is a methyl group and R^3 is hex-5-enyl group, and R^1 is other than a propyl, isobutyl, pentyl or hexyl group when R^2 is a methyl group and R^3 is a hex-5-enyl group.

Preferred compounds of formula I' are those in which R^2 is an alkenyl group having from 4 to 8 carbon atoms or an alkyl group having from 1 to 12 carbon atoms, and when R^2 is methyl and R^1 or R^3 is an (ω - 1)-alkenyl group unbranched in (ω - 1)-position, the sum of the carbon atoms of the alkyl substituents R^1 and R^2 is, however, greater than 7 or the sum of the carbon atoms of the alkyl substituents R^2 and R^3 is greater than 11.

Especially preferred compounds of the invention are those in which at least one of the radicals R^1, R^2 and R^3 represents an alkyl group having from 2 to 12 carbon atoms and at least one of them represents an alkenyl group, R^1 being alkyl, alkenyl or even hydrogen and one of the radicals possibly being methyl. Also especially preferred are compounds in which more than one of the groups R^1, R^2 and R^3 are alkenyl groups in which the double bond preferably is in the (ω - 1)-position. Another preferred embodiment relates to compounds in which the double bond is in a position other than the (ω - 1)-position.

According to a still further aspect of the present invention there are provided the following processes for the preparation of the novel alkenyl-xanthines of formula I':—

a) reacting a compound of formula I' in which at least one of R^1, R^2 and R^3 is hydrogen and the remainder of these groups is an alkyl and/or alkenyl group, optionally in the presence of a base or in the form of their salts, with a compound of formula

R——X

in which X represents a halogen, preferably a chlorine or bromine atom or a sulphonic acid ester or phosphoric acid ester group and R represents an alkenyl group having from 4 to 8 carbon atoms (for the introduction of one or more alkenyl groups) or an alkyl group having from 1 to 12 carbon atoms (for the introduction of one or more alkyl groups).

Thus, unsubstituted xanthine; 1-, 3- or 7-mono-xanthines or monoalkenyl-xanthines; or 1,3-, 1,7- or 3,7-dialkyl- or dialkenyl-xanthines or a corresponding monoalkyl-monoalkenyl-xanthine are used in this process. The alkyl and alkenyl groups may be straight-chained or branched, as desired.

The xanthine derivatives used in this process are preferably in the form of their alkali metal or alkaline-earth metal salts.

This process may be carried out in conventional manner, generally at a temperature of from 20 to 160°C, preferably from 35 to 125°C, and optionally at an elevated or reduced pressure, but usually at atmospheric pressure. The individual starting materials may be used in stoichiometric or, for economic reasons, in non-stoichiometric quantities. The reaction time is, of course, generally dependent on the temperature. The reaction may be completed after one hour, although the reaction time generally amounts to more than 6 hours.

The reaction is conveniently effected in the presence of an inorganic base such as, for example, an alkali metal or alkaline-earth metal hydroxide, carbonate, hydride or alcoholate, or an organic base such as triethylamine or tributylamine. Alkali metal or alkaline-earth metal salts of the starting xanthines are advantageously produced *in situ*.

The above process is conveniently effected

in the presence of a solvent. Convenient solvents are those which are miscible with water, and may be used in admixture with water, e.g. methanol, ethanol, propanol, isopropanol, the various butanols, acetone, pyridine, polyhydric alcohols such as ethylene glycol and ethylene glycol monomethyl or ethyl ether. Aprotic dipolar solvents such as formamide, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, tetramethyl-urea, hexamethylphosphoric acid trisamide and dimethylsulphoxide may also be used. In addition, hydrocarbon solvents such as benzene, toluene or xylene, as well as mixtures of the said solvents, if they are mutually miscible are also suitable.

This process enables the same or different alkenyl and/or alkyl substituents to be introduced in succession or several similar substituents can be linked to the xanthine nucleus without isolating any intermediate product in a coupled reaction.

b) reacting an appropriate oxoalkylxanthines with an olefinising agent, whereby the number of carbon atoms in the oxoalkyl group and in the group introduced with the olefinising agent is in total from 4 to 8 carbon atoms; or

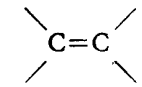
c) dehydrating an appropriate hydroxyalkyl-xanthine in which the hydroxyl alkyl group has from 4 to 8 carbon atoms.

Process b) may be effected by the conventional olefinising reactions, for example, according to Wittig-Horner (Houben-Weyl volume 5/1 b (1972), 383 *et seq*). Oxoalkylxanthines may be converted into corresponding alkenyl-xanthines according to the invention in solvents such as dioxan, dimethylformamide or dimethylsulphoxide, generally at temperatures of from 20 to 160°C, preferably of from 20 to 80°C, by reaction, for example, with a suitable phosphinyl alkylene. Branch-chained xanthine derivatives may also be obtained by this process.

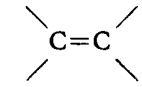
Dehydration of hydroxyalkyl-xanthines into alkenyl-xanthines according to process c) may be carried out by conventional techniques, for example, in the presence of acid catalysts, e.g. *p*-toluenesulphonic acid.

If 1,3,7 - trisubstituted - hydroxyalkylxanthines are used in process c), the Tschugaeff xanthane method is advantageously adopted, that is converting the hydroxyalkylxanthines preferably in benzene, ether or toluene solution *via* their alkali metal salts, preferably their sodium salts, by reaction with carbon disulphide and methyl iodide into methyl xanthates which are transformed at temperatures of 110 to 230°C into corresponding alkenyl-xanthines.

The process according to the invention enable those alkenyl-xanthines to be prepared in which the



grouping of the alkenyl group is bound directly to a nitrogen atom and also those in which the grouping



is separated by at least one, preferably 2 to 6 carbon atoms from the xanthine nucleus.

Examples of particular substances according to the invention which may be incorporated into the compositions according to the invention are:

1,3-dimethyl-7-(but-3-enyl)-xanthine;
1,3-dimethyl-7-(pent-4-enyl)-xanthine;
1,3-dimethyl-1-(hex-5-enyl)-xanthine;
1-(but-3-enyl-3-3,7-dimethyl-xanthine;
1-(pent-4-enyl-),7-dimethyl-xanthine;
1-(but-3-enyl)-3-methyl-7-*n*-propyl-xanthine;
1-(but-3-enyl)-3-methyl-7-*n*-hexyl-xanthine;
1-(hex-5-enyl)-3-methyl-7-*n*-propyl-xanthine;
1-(hex-5-enyl-3-methyl-7-*n*-hexyl-xanthine;
1-(hex-5-enyl)-3-methyl-7-*n*-decyl-xanthine;
1-ethyl-3-methyl-7-(hex-5-enyl)-xanthine;
1-*n*-propyl-3-methyl-7-(but-3-enyl)-xanthine;
1-*n*-hexyl-3-methyl-7-(but-3-enyl)-xanthine;
1-*n*-hexyl-3-methyl-7-(pent-4-enyl)-xanthine;
1-*n*-decyl-3-methyl-7-(but-3-enyl)-xanthine;
1-methyl-3-ethyl-7-(hex-5-enyl)-xanthine;
1,3-diethyl-7-(pent-4-enyl)-xanthine;
1,3-diethyl-1-(hex-5-enyl)-xanthine;
1,3-di-(*n*-butyl)-7-(but-3-enyl)-
3-methyl-7-(but-3-enyl)-xanthine;
3-methyl-7-(pent-4-enyl)-xanthine;
3-methyl-1-(hex-5-enyl)-xanthine;
3-ethyl-7-(but-3-enyl)-xanthine;
3-ethyl-7-(hex-5-enyl)-xanthine;
1,7-di-(but-3-enyl)-3-ethyl-xanthine;
1-(but-3-enyl)-3-ethyl-7-hex-5-enyl)-xanthine;
1-*n*-hexyl-3-methyl-7-(hex-5-enyl)-xanthine;
1,3-dimethyl-7-(5-methyl-hex-5-enyl)-xanthine;
1,3-dimethyl-7-(hex-4-enyl)-xanthine;
1-methyl-3-*n*-butyl-1-(oct-7-enyl)-xanthine;

3,7-di-(pent-4-enyl)-xanthine;
1,3,7-tri-(pent-4-enyl)-xanthine;
1-*n*-propyl-3-(hex-5-enyl)-7-n-hexyl-xanthine;
1-methyl-3-ethyl-7-(hept-6-enyl)-xanthine;
1,7-dimethyl-3-(pent-4-enyl)-xanthine;
1,3-di-(*n*-hexyl)-7-(but-3-enyl)-xanthine;
1,3-di-(*n*-butyl)-7-(hex-5-enyl)-xanthine;
1-(2-methyl-but-3-enyl)-3,7-dimethyl-xanthine;
1-(hex-5-enyl)-3-methyl-7-butyl and and 7-isobutyl-xanthine;
1,3-di-methyl-7-(2-methyl-but-3-enyl)-xanthine;
1,3-dimethyl-7-(hept-6-enyl)-xanthine;
1-propyl-, 1-isobutyl-, and 1-pentyl-3-methyl-7-(hex-5-enyl)-xanthine); and
1,7-di-(hex-5-enyl)-3-methyl-xanthine.

The compositions according to the invention have interesting physiological properties. They may be conveniently administered orally or rectally, e.g. in solid or dissolved forms. If the particular xanthine derivative according to the invention desired is readily soluble in water, it may also be administered parenterally.

If desired the compositions according to the invention may additionally comprise one or more further physiologically active ingredients, such as for example vitamins.

Suitable forms of administration of the compositions of the invention are, for example, solutions, emulsions, tablets, coated tablets, capsules, microcapsules, powders, syrups, suppositories, granulates or forms adapted to provide a sustained release of active ingredient, and these may be prepared in a manner known *per se* using excipients conventional therefor such as, for example, carriers; disintegrants; binders; coatings; swelling, sliding or lubricating agents; flavourings; sweeteners; agents providing a sustained release effect; and solubilising agents. Examples of such additives are lactose, mannitol, talcum, milk protein, starch, gelatin, cellulose or its derivatives such as methyl cellulose, hydroxyethyl cellulose or suitable swelling or non-swelling copolymers. By the use of extenders, which can be used in lesser or greater amounts, the decomposition of the preparation and, as a result the release of the active ingredient, may be controlled.

The compositions of the present invention may be presented in the form of injectible solutions of compounds of general formula I in sterile water, e.g. in double distilled water. As indicated above they may also be in a solid form preferably in dosage unit form, if desired in a form giving delayed release of the active ingredient(s).

Dosage unit formulations of the compositions preferably contain, according to the particular degree of activity, from 10 to 1000 mg, generally up to 400 mg and especially up to 200 mg, of the active ingredient of formula I. Thus, the average quantity of the compounds of formula I administered is in the range of 0.2 to 20 mg per kg of body weight.

Dosage units may be administered once or several times daily, the number of administrations depending on the particular content of active ingredient and on the type of administration. More frequent administration is recommended if for example the dosage unit has only a small content of active substance; but on the other hand if the content is relatively high, the compositions may be administered only for example once a day. If, further, the composition is supplied in sustained release form, administration may be restricted to at least once a day. The length of time over which administration may be effected during treatment may range from one to several weeks, although if necessary and/or desired the compositions may be administered over much longer periods.

The compositions of the invention have interesting physiological properties, in particular a blood circulation-assisting activity, and also a low toxicity. Thus, the compositions are of value for increasing cerebrovascular circulation.

Investigation of brain circulation in cats.

A heat-conduction probe was used to measure local brain circulation (in the cortex). The method necessary to measure heat conduction was adopted in detail from the experiments described by Betz *et al.* in

(1) Betz *et al.*: Pflügers Arch. ges. Physiol. *288*, 389 (1966),
(2) Priebe, L. *et al.*: Pflügers Arch. ges. Physiol. *294*, 3, 26 (1967),
(3) Betz, E.: Symposium der Dtsch. Ges. f. Angiologie, 6, Jahrestagung, Munich (1968),
(4) Betz, E.: Pflügers Arch. ges. Physiol. *284*, 3, 278 (1965),
(5) Betz, E.: Acta Neurol. Scand., Suppl. *14*, 29, (1965),
(6) Betz, E.: Physiological Rev. *52*, 3 (1972).

The tests were conducted on anesthetised cats (sodium pentabaribital 35 mg/kg body weight i.p.). Blood pressure was measured in a femoral artery using a Statham device.

Table 1 indicates for some of the alkenylxanthines according to the invention prepared, the duration of activity as a half-value time (HVT) and the intensity of activity as the difference in the heat-conduction number λ ($\Delta\lambda = \lambda_{after} - \lambda_{before}$) in comparison with corresponding values for the vasotherapeutic product aminophylline. The results indicate

that the substances contained in the compositions according to the invention have a superiority both in the intensity of the effect and in the duration of activity from fluvographic measurement of brain circulation in cats.

TABLE 1

Activity of various alkenyl xanthines and aminophyllin on brain circulation in cats

Substance	Dose in mg/kg i.v.	Change in blood perfusion Δλ	HVT [min]
Example 1	2	+3	0.5
	5	+4.5	2
Example 2	2	+4.5	2
	5	+4.2	4
Example 3	2	+2.2	10
	5	+6	15
Example 4	2	+7.3	5
	5	+7.5	3
Example 5	2	+3.3	1
	5	+3.7	5
Aminophylline (Comparison)	1	+0.19	1.8
	2	+0.15	1.8
	5	+0.18	3.3
	10	+0.53	1.7

The following Examples serve to illustrate the preparation of compounds according to the invention. In these Examples the ratios relate to volume ratios.

Example 1.

1,3-Dimethyl-7-(but-3-enyl)-xanthine.

13.9 g of 4 - bromo - but - 1 - ene are reacted with 20.2 g of sodium theophilline in 200 ml of dimethylformamide at 120°C with stirring for approximately 6 to 8 hours until the reaction is complete as indicated by thin-layer chromatography. The solvent is then removed under reduced pressure. The residue is dissolved at 20°C in 100 ml of methylene chloride, separated from insoluble sodium bromide and purified through a column packed with neutral aluminium oxide to remove small quantities of dark-coloured accompanying substances. Melting point: 110°C (acetone); yield: 21.6 g (91% of theory relative to the starting material used). After thin-layer chromatography on Merck DC finished plates of silica gel 60 F_{254} with benzene/acetone (6:4) as eluent, the product has an R_f value of 0.54; and with nitromethane/benzene/pyridine (20:10:3) as eluent, an R_f value of 0.65. Ultra-violet light was used as indicator, though the pyridine of the eluent must, however, be removed at 50°C under reduced pressure because of its ability to extinguish fluorescence.

Examples 2 to 5.

The following compounds are prepared analagously to Example 1 from the corresponding dimethyl compounds:

2. 1,3 - Dimethyl - 7 - (pent - 4 - enyl)-xanthine.
3. 1,3 - Dimethyl - 7 - (hex - 5 - enyl)-xanthine.
4. 1 - (But - 3 - enyl) - 3,7 - dimethyl-xanthine.

5. 1 - (Pent - 4 - enyl) - 3,7 - dimethyl-xanthine.

The physical data of these compounds are set out in Table 2.

Example 6.
1-(But-3-enyl)-3-methyl-7-*n*-propyl-xanthine.

20.8 g of 3 - methyl - 7 - *n* - propyl-xanthine, 13.8 g of anhydrous potassium carbonate and 13.5 g of 4 - bromo - 1 - ene are refluxed for 8 hours in 150 ml of dimethylformamide, and the solvent is then removed under reduced pressure. The residue is then dissolved in 150 ml of 1-N sodium hydroxide solution and the alkaline solution is extracted with methylene chloride. The residue obtained after separation and evaporation of the methylene chloride is triturated with 100 ml of diisopropyl ether and unreacted 3 - methyl-7 - *n* - propyl - xanthine is removed. 15.6 g (70% of theory) of the *title compound* of melting point 48°C (from *n*-hexane) are obtained from the filtrate.

Examples 7 to 10.

The following compounds are prepared analogously to Example 6 from the corresponding dialkyl-xanthine compounds:

7. 1 - (But - 3 - enyl) - 3 - methyl - 7-hexyl - xanthine.
8. 1 - (Hex - 5 - enyl) - 3 - methyl - 7-propyl - xanthine.
9. 1 - (Hex - 5 - enyl) - 3 - methyl - 7-hexyl - xanthine.
10. 1 - (Hex - 5 - enyl) - 3 - methyl - 7-decyl - xanthine.

The physical data of the compounds are set out in Table 2.

Example 11.
1-Ethyl-3-methyl-7-(hex-5-enyl)-xanthine.

20 g of 3 - methyl - 7 - (hex - 5 - enyl)-xanthine (see Example 22) are added to a solution of approximately 3.3 g of NaOH in 70 ml of methanol/water (1:1) and subsequently 9 g of ethyl bromide are added thereto. The mixture is kept at 40°C under a nitrogen atmosphere for 40 hours. The solvent is then removed under reduced pressure, the residue dissolved in diethyl ether and the pH of the solution is adjusted with aqueous sodium hydroxide solution to a value of 13.5 to remove unreacted 3 - methyl - 7 - (hex - 5 - enyl)-xanthine. 1 - Ethyl - 3 - methyl - 7 - (hex-5 - enyl) - xanthine is then obtained from the ether phase as a colourless oil by column chromatography using silica gel with methylene chloride/acetone (8:2) as eluent followed by distillation under reduced pressure. Yield: 11.2 g (81.3% of theory of the *title compound*, $n_D^{20} = 1.5415$.

Example 12.
1-Propyl-3-methyl-7-(but-3-enyl)-xanthine.

The *title compound* is prepared analogously to Example 11 from 3 - methyl - 7 - (but-3 - enyl) - xanthine (see Example 20), but with the difference that the reaction temperature is 70°C.

Examples 13 and 14.

1 - Hexyl - 3 - methyl - 7 - (but - 3-enyl) - xanthine and 1 - Hexyl - 3 - methyl-7 - (pent - 4 - enyl) - xanthine are prepared analogously to Example 1.

Example 15.

1 - Decyl - 3 - methyl - 7 - (but - 3-enyl - xanthine is prepared analogously to Example 12.

Example 16.

1 - Methyl - 3 - ethyl - 7 - (hex - 5-enyl) - xanthine is prepared analogously to Example 11 from 3 - ethyl - 7 - (hex - 5-enyl) - xanthine (see Example 24).

Example 17.

1,3 - Diethyl - 7 - (pent - 4 - enyl)-xanthine is prepared analogously to Example 12 from 1,3 - diethyl - xanthine and 5-bromopent - 1 - ene: the yield relative to the starting material used is given in Table 2.

Example 18.

1,3 - Diethyl - 7 - (hex - 5 - enyl)-xanthine is prepared analogously to Example 12 from 1,3 - diethyl - xanthine; the yield relative to the starting material used is given in Table 2.

Example 19.
1,3-Di-*n*-butyl-7-(but-3-enyl)-xanthine.

38.9 g of 1,3 - di - *n* - butyl - xanthine are added at 25°C to a solution of 3.4 g of sodium in 200 ml of absolute ethanol. 20.5 g of 4 - bromo - but - 1 - ene are then added at 50°C. After stirring for 46 hours under a nitrogen atmosphere at 70°C the reaction mixture is cooled to 20°C, precipitated sodium bromide is filtered off and the filtrate is then evaporated under reduced pressure. The residue obtained is treated with chloroform and 1-N sodium hydroxide solution to remove 1,3-di - *n* - butyl - xanthine. From the chloroform phase there is obtained a yellow oily residue which after column chromatography on silica gel with methylene chloride/acetone (8:2) as eluent and after distillation under reduced pressure yields 29.7 g (78.8% of theory) of the *title compound* with a melting point of 41 to 42°C.

Example 20.

3-Methyl-7-(but-3-enyl)-xanthine.

41.5 g of 3 - methyl -xanthine are added with stirring at 70°C to a solution of 10.2 g of NaOH in 400 ml of methanol/water (1:1). After mixing with 35.1 g of 4 - bromo - but-1 - ene the mixture is stirred under a nitrogen atmosphere for 27 hours at 70°C. The reaction mixture is then cooled to 20°C and the precipitate formed is filtered off. By re-precipitatio from alkaline solution (pH 13.5) and acidification with dilute sulphuric acid to pH 10, 29.6 g (89.7% of theory) of the *title compound* of melting point 245 to 246°C are obtained after drying.

Example 21.

3 - Methyl - 7 - (pent - 4 - enyl) - xanthine is prepared analogously to Example 1.

Examples 22 to 24.

3 - Methyl - 7 - (hex - 5 - enyl) - xanthine, 3 - Ethyl - 7 - (but -3 - enyl) - xanthine and 3 - Ethyl - 7 - (hex - 5 - enyl) - xanthine are prepared analogously to Example 20 from the corresponding alkyl-xanthines.

Example 25.

1,7 - Dimethyl - 3 - (hex - 5 - enyl)-xanthine is prepared analogously to Example 6 from 1,7 - dimethylxanthine and 6 - bromo-hex - 1 - ene.

Example 26.

1,7 - Di - (but - 3 - enyl) - 3 - ethyl-xanthine is prepared analogously to Example 12 from

a) 1 mol of 3 - ethyl - 7 - (but - 3 - enyl)-xanthine and 1 mol of 4 - bromobut - 1 - ene (yield: 83% of theory relative to reacted 3-ethyl - 7 - (but - 3 - enyl) - xanthine); and

b) 1 mol of 3 - ethyl - xanthine and 2 mol of 4 - bromobut - 1 - ene (yield: 39% of theory relative to reacted 3 - ethyl - xanthine.

Example 27.

1 - (But - 3 - enyl) - 3 - ethyl - 7 - (hex-5 - enyl) - xanthine is prepared analogously to Example 12 from 3 - ethyl - 7 - (hex - 5-enyl) - xanthine and 4 - bromobut - 1 - ene (yield: 71.6% of theory relative to reacted 3 - ethyl - 7 - (hex - 5 - enyl) - xanthine).

Example 28.

1 - Hexyl - 3 - methyl - 7 - (hex - 5-enyl) - xanthine is prepared analogously to Example 1.

Example 29.

1,3-Dimethyl-7-(5-methyl-hex-5-enyl)-xanthine.

0.5 g of sodium hydride in 15 ml of anhydrous dimethylsulphoxide are reacted under a nitrogen atmosphere with stirring at 80°C and cooled to 15°C after 25 minutes. To prepare triphenyl - methylene - phosphorane, 8.1 g of methyl-triphenyl phosphonium iodide in 20 ml of anhydrous dimethylsulphoxide are added to this solution. After stirring for 10 minutes at room temperature, 5.6 g of 1,3-dimethyl - 7 - (5 - oxohexyl) - xanthine in 10 ml of dimethylsulphoxide are added dropwise over 10 minutes, and the temperature is not allowed to exceed 20°C. After standing overnight, the mixture is dissolved in water, extracted with ether and the ether phase is separated and dried over Na_2SO_4. The product obtained after evaporation at reduced pressure is in the form of an oil following purification by column chromatography on silica gel with methylene chloride/acetone (1:1) as eluent and distillation under reduced pressure. Yield: 3.5 g (63.3% of theory relative to the starting product used); refractive index: n_D^{20} 1.5445.

Example 30.

1,3-Dimethyl-7-(hex-4-enyl)-xanthine.

7 g of 1,3 - dimethyl - 7 - (5 - hydroxy-hexyl) - xanthine and 9.5 g of *p*-toluene sulphonic acid are refluxed in 100 ml of toluene for 12 hours with continuous separation of the water formed in the reaction. After cooling to room temperature the reaction mixture is mixed with 100 ml of ether, washed with sodium bicarbonate solution and water until neutral and the organic phase separated, dried over sodium sulphate and evaporated under reduced pressure. After column chromatography on silica gel with methylene chloride/acetone (1:1) as eluent and distillation under reduced pressure the residue gives a product which still contains a few percent of isomeric 1,3 - dimethyl - 7 - (hex-5 - enyl) - xanthine (as shown by the n.m.r. spectrum). Yield: 4.3 g (65.5% of theory relative to the starting product used). Melting point: 58—64°C.

Example 31.

1 - (Hex - 5 - enyl) - 3,7 - dimethyl-xanthine is prepared analogously to Example 1.

Examples 32 and 33.

1 - (Hex - 5 - enyl) - 3 - ethyl - 7-methyl - xanthine and 1 - (Pent - 4 - enyl)-3 - ethyl - 7 - methyl - xanthine are prepared analogously to Example 12.

Example 34.

1,3 - Dimethyl - 7 - (2 - methyl - pent-2 - enyl) - xanthine is prepared analogously to Example 29.

Example 35.

Preparation of coated tablets.

1000 coated tablets are prepared from the following ingredients:—

1,3-dimethyl-7-(hex-5-enyl)-xanthine	100 g
lactose	20 g
maize starch	30 g
talc	8.5 g
colloidal silicic acid	0.5 g
magnesium stearate	1.0 g

The above ingredients are mixed together and pressed into tablet cores, each weighing 160 mg. The cores are then coated with a mixture containing 44.57 g of cane sugar, 25.4 g of talc, 8 g of cellulose acetate phthalate, 2.24 g of castor oil and very small quantities of wax, titanium dioxide and gum arabic, in such a way that the final weight of the coated tablets is 240 mg.

The following Table 2 provides details of the products of Examples 1 to 34.

TABLE 2

Ex.	compound 1	3	7-position	mp. °C	recry. from	b.p. °C/mbar	Rf	n_D^{20}	yield	sum formula mol weight	analysis calc. found.
1	CH_3	CH_3	but-3-enyl	110	acetone		1)0.54 2)0.65		91%	$C_{11}H_{14}N_4O_2$ 234.3	C 56.4 H 6.0 N 23.9 C 56.3 H 6.0 N 23.8
2	CH_3	CH_3	pent-4-enyl	92	hexane		1)0.66 2)0.52		92%	$C_{12}H_{16}N_4O_2$ 248.3	C 58.1 H 6.5 N 22.6 C 58.1 H 6.3 N 22.7
3	CH_3	CH_3	hex-5-enyl	42	hexane		1)0.61 2)0.67		94%	$C_{13}H_{18}N_4O_2$ 262.3	C 59.5 H 6.9 N 21.4 C 59.4 H 6.9 N 21.6
4	but-3-enyl	CH_3	CH_3	115	acetone		1)0.52 2)0.50		93%	$C_{11}H_{14}N_4O_2$ 234.3	C 56.4 H 6.0 N 23.9 C 56.5 H 5.9 N 24.0
5	pent-4-enyl	CH_3	CH_3	94	hexane		1)0.54 2)0.46		91%	$C_{12}H_{16}N_4O_2$ 248.3	C 58.1 H 6.5 N 22.6 C 58.1 H 6.6 N 22.6
6	but-3-enyl	CH_3	propyl	48	hexane		4)0.77		70%	$C_{13}H_{18}N_4O_2$ 262.3	C 59.5 H 6.9 N 21.4 C 59.7 H 7.0 N 21.3
7	but-3-enyl	CH_3	hexyl			190 °1.1	4)0.68	1.5310	80%	$C_{16}H_{24}N_4O_2$ 304.4	C 63.1, H 7.9 N 18.4 C 63.0 H 8.1 N 18.5
8)	hex-5-enyl	CH_3	propyl	43	++)		4)0.67		81%	$C_{15}H_{22}N_4O_2$ 290.4	C 62.0 H 7.6 N 19.3 C 62.2 H 7.8 N 19.7
9	hex-5-enyl	CH_3	hexyl			195/0.33	4)0.82	1.5265	75%	$C_{18}H_{28}N_4O_2$ 332.5	C 65.0 H 8.5 N 16.9 C 64.7 H 8.6 N 17.1
10	hex-5-enyl	CH_3	decyl	39	++)		4)0.87		69%	$C_{22}H_{36}N_4O_2$ 388.6	C 68.0 H 9.3 N 14.4 C 68.3 H 9.5 N 14.5
11	C_2H_5	CH_3	hex-5-enyl				3)0.71	1.5415	81%	$C_{14}H_{20}N_4O_2$ 276.3	C 60.9 H 7.3 N 20.3 C 60.6 H 7.4 N 20.2

TABLE 2 (Continued)

Ex.	compound 1-	3-	7-position	mp. °C	recry. from	b.p. °C/mbar	Rf	n_D^{20}	yield	sum formula mol weight	analysis calc: found:
12	Propyl	CH_3	but-3-enyl	55–56					71%	$C_{13}H_{18}N_4O_2$ 262.3	C 59.5 H 6.9 N 21.4 C 59.6 H 7.1 N 21.6
13	Hexyl	CH_3	but-3-enyl	+) 92	diethyl-ether		1)0.54 2)0.58		89%	$C_{16}H_{25}ClN_4O_2$ 340.9	C 56.4 H 7.4 N 16.4 C 56.5 H 7.3 N 16.6
14	Hexyl	CH_3	pent-4-enyl	+)98	diethyl-ether		1)0.54 2)0.61		92%	$C_{17}H_{27}ClN_4O_2$ 354.9	C 57.5 H 7.7 Cl 10.0 N 15.6 C 57.6 H 7.7 Cl 10.2 N 15.7
15	Decyl	CH_3	but-3-enyl	74	white spirit				82%	$C_{20}H_{32}N_4O_2$ 360.5	C 66.6 H 9.0 N 15.5 C 66.5 H 9.0 N 15.3
16	CH_3	C_2H_5	hex-5-enyl				3)0.81	1.5400	89%	$C_{14}H_{20}N_4O_2$ 276.3	C 60.8 H 7.3 N 20.3 C 60.6 H 7.4 N 20.5
17	C_2H_5	C_2H_5	pent-4-enyl				3)0.9	1.5384	84%	$C_{14}H_{20}N_4O_2$ 276.3	C 60.8 H 7.3 N 20.3 C 60.8 H 7.4 N 20.3
18	C_2H_5	C_2H_5	hex-5-enyl				3)0.94	1.5345	79%	$C_{15}H_{22}N_4O_2$ 290.4	C 62.1 H 7.6 N 19.3 C 61.8 H 7.7 N 19.0
19	Butyl	butyl	but-3-enyl	41–42					79%	$C_{17}H_{26}N_4O_2$ 318.4	C 64.1 H 8.2 N 17.6 C 63.9 H 8.1 N 17.5
20		CH_3	but-3-enyl	245–246					90%	$C_{10}H_{12}N_4O_2$ 220.2	C 54.5 H 5.5 N 25.4 C 54.3 H 5.4 N 25.4
21		CH_3	pent-4-enyl	202	methanol/H_2O		1)0.50 2)0.27		87%	$C_{11}H_{14}N_4O_2$ 234.3	C 56.4 H 6.0 N 23.9 C 56.5 H 5.9 N 23.8
22		CH_3	hex-5-enyl	206					83%	$C_{12}H_{16}N_4O_2$ 248.3	C 58.1 H 6.5 N 22.6 C 57.9 H 6.6 N 22.5

TABLE 2 (Continued)

Ex.	compound 1-	3-	7-position	m.p. °C	recry. from	b.p. °C/mbar	Rf	n_D^{20}	yield	sum formula mol weight	analysis calc: found:
23		C_2H_5	but-3-enyl	146–147					81%	$C_{11}H_{14}N_4O_2$ 234.3	C 56.4 H 6.0 N 23.9 C 56.2 H 6.0 N 24.1
24		C_2H_5	hex-5-enyl	130					85%	$C_{13}H_{18}N_4O_2$ 262.3	C 59.5 H 6.9 N 21.4 C 59.6 H 6.9 N 21.6
25	CH_3	hex-5-enyl	CH_3	69–70	++)				75%	$C_{13}H_{18}N_4O_2$ 262.3	C 59.5 H 6.9 N 21.4 C 59.6 H 6.9 N 21.3
26	but-3-enyl	C_2H_5	but-3-enyl	63					a)83% b)39%	$C_{15}H_{20}N_4O_2$ 288.4	C 62.5 H 7.0 N 19.4 C 62.7 H 7.1 N 19.5
27	but-3-enyl	C_2H_5	hex-5-enyl				3)1.0	1.5350	72%	$C_{17}H_{24}N_4O_2$ 316.4	C 64.5 H 7.7 N 17.7 C 64.6 H 7.8 N 17.9
28	Hexyl	CH_3	hex-5-enyl			193/0.4			92%	$C_{18}H_{28}N_4O_2$ 332.5	C 65.0 H 8.5 N 16.9 C 64.7 H 8.2 N 16.9
29	CH_3	CH_3	5-CH_3-hex-5-enyl					1.5445	63%	$C_{14}H_{20}N_4O_2$ 276.3	C 60.8 H 7.3 N 20.3 C 60.9 H 7.3 N 20.3
30	CH_3	CH_3	hex-4-enyl	58–64					65%	$C_{13}H_{18}N_4O_2$ 262.3	C 59.5 H 6.9 N 21.4 C 59.6 H 7.1 N 21.5
31	hex-5-enyl	CH_3	CH_3	76–77	hexane		1)0.47 2) 0.60		92%	$C_{13}H_{18}N_4O_2$ 262.3	C 59.5 H 6.9 N 21.4 C 59.6 H 7.1 N 21.2
32	hex-5-enyl	C_2H_5	CH_3	64					75%	$C_{14}H_{20}N_4O_2$ 276.3	C 60.9 H 7.3 N 20.3 C 60.6 H 7.2 N 20.2

TABLE 2 (Continued)

Ex.	compound 1-	3-	7-position	mp. °C	recry. from	b.p. °C/mbar	Rf	n_D^{20}	yield	sum formula mol weight	analysis calc: found
33	pent-4-enyl	C_2H_5	CH_3					1,5460	78%	$C_{13}H_{18}N_4O_2$ 262.3	C 59.5 H 6.9 N 21.4 C 59.4 H 7.0 N 21.4
34	CH_3	CH_3	2-CH_3-pent-2-enyl	104-106	++)				55%	$C_{13}H_{18}N_4O_2$ 262.3	C 59.5 H 6.9 N 21.4 C 59.6 H 7.0 N 21.6

Remarks

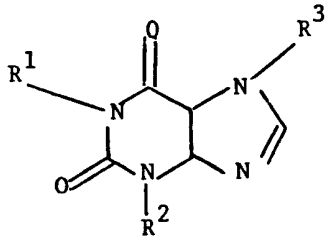
) values as hydrochloride
) diisopropyl ether

eluent: thin-layer chromatography

1) = benzene/acetone (6.4)
2) = nitromethane/Benzene-pyridine (20.10.3)
3) = toluene/acetone (7:3) (all values in relation to example 27 - 1.0)
4) = chloroform/benzene/acetone (1:1:1)

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising as active ingredient at least one compound of formula



(I)

(wherein R^1 represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or an alkenyl group having from 4 to 8 carbon atoms; and R^2 and R^3, which may be the same or different, each represents an alkyl group having from 1 to 12 carbon atoms or an alkenyl group having from 4 to 8 carbon atoms; with the proviso that at least one of R^1, R^2 and R^3 represents an alkenyl group having from 4 to 8 carbon atoms) in association with a pharmaceutical carrier or excipient.

2. A composition as claimed in claim 1 wherein at least one of R^1, R^2 and R^3 in the compound of formula I is an $(\omega - 1)$ - alkenyl group.

3. A composition as claimed in claim 1 wherein one of R^1, R^2 and R^3 in the compound of formula I is an $(\omega - 1)$ - alkenyl group in which the carbon atom at the double bond is separated from the xanthine nucleus by at least one saturated carbon atom and the remainder of R^1, R^2 and R^3 are both methyl groups but R^1 may also be a hydrogen atom.

4. A composition as claimed in claim 1 wherein one of R^1 and R^3 in the compound of formula I is a straight-chained $(\omega - 1)$-alkenyl group having from 4 to 8 carbon

atoms and the other is a methyl group.

5. A composition as claimed in any of the preceding claims wherein the alkenyl group has from 5 to 8 carbon atoms.

6. A composition as claimed in any of the preceding claims in a form suitable for oral, rectal or parenteral administration.

7. A composition as claimed in claim 6 in the form of solutions, emulsions, tablets, coated tablets, capsules, granulates, powders, syrups, suppositories or forms adapted to provide a sustained release of active ingredient.

8. A composition as claimed in any of the preceding claims in dosage unit form.

9. A composition as claimed in claim 8 wherein each dosage unit comprises from 10 to 1000 mg of said active ingredient.

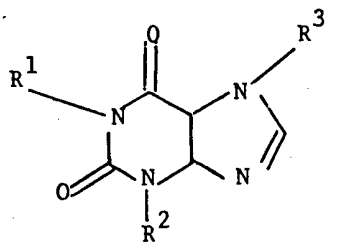
10. A composition as claimed in claim 8 wherein each dosage unit comprises up to 400 mg of said active ingredient.

11. A composition as claimed in claim 9 wherein each dosage unit comprises up to 200 mg of said active ingredient.

12. A composition as claimed in any of the preceding claims additionally comprising at least one further physiologically active ingredient.

13. A composition as claimed in claim 1 substantially as herein described.

14. Compounds of general formula



(I')

wherein R^1 represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms or an alkenyl group having from 4 to 8 carbon atoms; and R^2 and R^3, which may be the same or different, each represents an alkyl group having from 1 to 12 carbon atoms or an alkenyl group having from 4 to 8 carbon atoms; with the provisos that at least one of R^1, R^2 and R^3 represents an alkenyl group having from 4 to 8 carbon atoms, R^1 is other than a but-3-enyl, pent-4-enyl or 2 - methyl-but - 3 - enyl group when R^2 and R^3 both represent methyl groups, R^1 is other than a hex-5-enyl group when R^2 represents a methyl group and R^3 represents a methyl, ethyl, propyl, butyl, isobutyl, decyl or hex-5-enyl group, R^1 is other than a methyl group when R^2 is a methyl group and R^3 is a 2 - methyl-but - 3 - enyl group, but-3-enyl, pent-4-enyl, hex-5-enyl or hept-6-enyl group, R^1 is other than a hydrogen atom when R^2 is a methyl group and R^3 is a hex-5-enyl group, and R^1 is other than a propyl, isobutyl, pentyl or hexyl group when R^2 is a methyl group and R^3 is a hex-5-enyl group.

15. Compounds as claimed in claim 14 wherein R^2 represents an alkyl group having from 1 to 12 carbon atoms or an alkenyl group having from 4 to 8 carbon atoms and when R^2 is a methyl group and R^1 or R^3 is an $(\omega - 1)$ - alkenyl group unbranched in the $(\omega - 1)$ - position, the sum of the carbon atoms of the alkyl substituents R^1 and R^2 is greater than 7 and the sum of the carbon atoms of the alkyl substituents R^2 and R^3 is greater than 11.

16. Compounds as claimed in claim 14 wherein at least one of the radicals R^1, R^2 and R^3 represents an alkyl group having from 2 to 12 carbon atoms and at least one of them represents an alkenyl group, R^1 being alkyl, alkenyl or even hydrogen and one of the radicals possibly being methyl.

17. Compounds as claimed in claim 14 wherein more than one of the groups R^1, R^2 and R^3 each represents an alkenyl group in which the double bond is in the $(\omega - 1)$-position.

18. Compounds of formula I' as defined in claim 14 as herein specifically disclosed.

19. A process for the preparation of compounds of formula I' as defined in claim 14 which comprises reacting a compound of formula I' in which at least one of R^1, R^2 and R^3 represents a hydrogen atom and the remainder of R^1, R^2 and R^3 is as defined in claim 14, or a salt thereof, with a compound of formula

$$R\text{——}X$$

[in which X represents a halogen atom or a sulphonic acid ester or phosphoric acid ester group, and R represents an alkenyl group having from 4 to 8 carbon atoms (for the introduction of one or more alkenyl groups) or an alkyl group having from 1 to 12 carbon atoms (for the introduction of one or more alkyl groups).

20. A process as claimed in claim 19 wherein X represents a chlorine or bromine atom.

21. A process as claimed in either of claims 19 and 20 wherein the reaction is effected at a temperature of from 20 to 160, preferably 35 to 125°C.

22. A process as claimed in any of claims 19 to 21 wherein the reaction is effected in the presence of a base.

23. A process as claimed in claim 22 wherein the base comprises an alkali metal or alkaline earth metal hydroxide, carbonate, hydride or alcoholate; triethylamine or tributylamine.

24. A process as claimed in any of claims 19 to 23 wherein the starting compound of formula I' is in the form of an alkali metal or alkaline earth metal salt.

25. A process as claimed in any of claims 19 to 24 wherein the reaction is effected in the presence of a solvent selected from solvents miscible with water in admixture with water, aprotic dipolar solvents, hydrocarbon solvents and mixtures thereof.

26. A process for the preparation of compounds of formula I′ as defined in claim 14 which comprises reacting an appropriate oxoalkyl-xanthine with an olefinising agent whereby the number of carbon atoms in the oxoalkyl group of the oxoalkyl-xanthine and in the group introduced with the olefinising agent is in total from 4 to 8 carbon atoms.

27. A process as claimed in claim 26 wherein the olefinisation reaction is effected by reacting the oxoalkyl-xanthine with a suitable phosphinyl alkylene.

28. A process as claimed in either of claims 26 and 27 wherein the reaction is effected in the presence of a solvent selected from dioxan, dimethylformamide and dimethylsulphoxide.

29. A process as claimed in any of claims 26 to 28 wherein the reaction is effected at a temperature of from 20 to 160°C, preferably 20 to 80°C.

30. A process for the preparation of compounds of formula I′ as defined in claim 14 which comprises dehydrating an appropriate hydroxyalkyl-xanthine in which the hydroxyalkyl group has from 4 to 8 carbon atoms.

31. A process as claimed in claim 30 wherein the dehydration is effected in the presence of an acid catalyst.

32. A process for the preparation of compounds of general formula I′ as defined in claim 14 substantially as herein described.

33. A process for the preparation of compounds of general formula I′ as defined in claim 14 substantially as herein described in any of the Examples.

34. A compound of formula I′ as defined in claim 14 whenever prepared by a process as claimed in any of claims 19 to 33.

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